



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/00, 31/48	A1	(11) International Publication Number: WO 98/52542 (43) International Publication Date: 26 November 1998 (26.11.98)
(21) International Application Number: PCT/US98/10155 (22) International Filing Date: 18 May 1998 (18.05.98) (30) Priority Data: 9710496.2 21 May 1997 (21.05.97) GB 9803990.2 25 February 1998 (25.02.98) GB (71) Applicant (for all designated States except US): MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M Center, P.O. Box 33427, Saint Paul, MN 55133-3427 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): OLIVER, Martin, J. [GB/GB]; 37 St. Leonards Road, Clarendon Park, Leicester LE2 1WS (GB). FATANIA, Kanu, M. [GB/GB]; 32 Leopold Street, Loughborough, Leicestershire LE11 5DL (GB). SCOTT, John, S. [GB/GB]; 12 Waver Close, Loughborough, Leicestershire LE11 2LG (GB). MULLER, Helgert [DE/DE]; Lerchental 1A, D-78315 Radolfzell (DE). (74) Agents: RINGSRED, Ted, K. et al.; Minnesota Mining and Manufacturing Company, Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: MEDICINAL AEROSOL PRODUCTS (57) Abstract <p>A pharmaceutical aerosol formulation suitable for oral and/or nasal inhalation including the anti-inflammatory drug ciclesonide, hydrofluorocarbon propellants such as HFC 134a and/or 227, and ethanol in an amount sufficient to solubilize the ciclesonide (and various optional ingredients, such as surfactant). The formulations exhibit very desirable physical and chemical stability, as well as excellent delivery characteristics.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

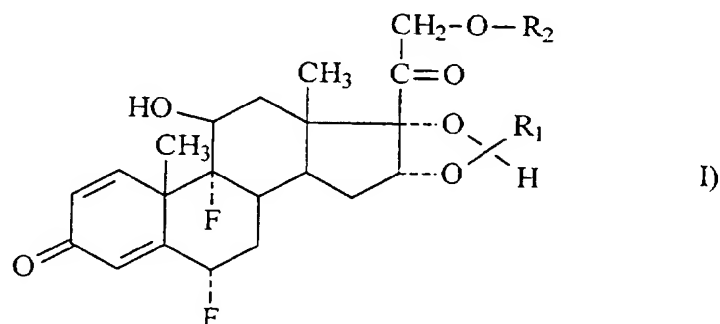
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

MEDICINAL AEROSOL PRODUCTS

This invention relates to medicinal aerosol products and in particular to medicinal products containing a pregna-1,4,diene-3,20-dione-16-17-acetal-21 ester, suitable for administration by inhalation.

5 GB-2247680 discloses pregna-1,4-diene-3,20-dione-16-17-acetal-21 esters and their use in the treatment of inflammatory conditions.

The compounds have the general structure:-



wherein R₁ is 2-propyl, 1-butyl, 2-butyl, cyclohexyl or phenyl; and
R₂ is acetyl or isobutanoyl.

10 Ciclesonide is 11 β , 16 α , 17, 21-tetrahydroxypregna 1,4-diene-3,20-dione, cyclic 16,17-acetal with cyclohexanecarboxaldehyde, 21-isobutyrate having the structure of formula (I) without fluorine atoms and in which R₁ is cyclohexyl and R₂ is isobutanoyl. This compound has undergone evaluation as an antiasthmatic and pharmacokinetic studies show that it will be useful in an inhaler formulation.
15 Ciclesonide is only moderately absorbed after oral administration and has low systemic activity. Concentration of the drug in the lungs is high and metabolism by liver oxidases is very high, giving the drug a low plasma half-life. Systemic activity of ciclesonide is three times lower than that of budesonide but anti-inflammatory activity is higher for the former.

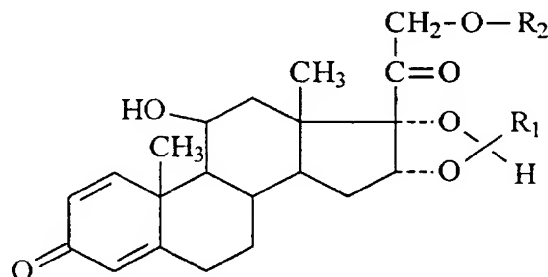
20 GB-2247680 proposes a specific pressurised aerosol formulation for delivering ciclesonide for oral and nasal inhalation. The disclosed formulation consists of ciclesonide as a micronized suspension of particles, sorbitan trioleate surfactant, and a mixture of three CFC propellants: trichloro-fluoromethane,

dichlorotetrafluoromethane, and dichlorodifluoromethane. However these CFC propellants are now believed to provoke the degradation of stratospheric ozone and there is a need to provide aerosol formulations for medicaments which employ so-called "ozone-friendly" propellants.

5 A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise hydrofluorocarbons and a number of medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777, W091/04011, W091/11173, W091/11495, W091/14422, WO93/11743, and EP-0553298. These
10 applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome problems associated with the use of this new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared. The applications propose, for example, the addition of one or more of adjuvants such as alcohols,
15 alkanes, dimethyl ether, surfactants (including fluorinated and non-fluorinated surfactants, carboxylic acids, polyethoxylates etc.).

 However, despite the various approaches used in formulating drugs for use in aerosol inhalation, there are still many serious difficulties and uncertainties often encountered in attempting to develop a physically and chemically stable CFC-free
20 formulation that reliably delivers an accurate dose of drug having the proper particle size range. In particular, there is a need for a CFC-free medicinal aerosol product containing ciclesonide (or similar molecules) that is chemically and physically stable and that is suitable for delivery to the respiratory system of a patient.

It has now been surprisingly found that, rather than the prior art approach of formulating ciclesonide as a suspension, ciclesonide can be very beneficially formulated as a physically and chemically stable solution in formulations including hydrofluorocarbon propellants. According to the present invention there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula:



in which:

R_1 is 1-butyl, 2-butyl, cyclohexyl or phenyl and

R_2 is acetyl or isobutanoyl, and a hydrofluorocarbon propellant, preferably propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof, and cosolvent, preferably ethanol, in an amount effective to solubilize the compound of formula (I) and optionally a surfactant.

The compounds of formula (I) is preferably ciclesonide and is generally present at a concentration of from 1 to 8 mg/ml, preferably 1 to 5 mg/ml.

The formulation generally comprises from 3 to 25% preferably 5 to 20%, more preferably 7 to 12% by weight ethanol.

The propellant preferably includes a hydrofluoralkane, in particular Propellant 134a, Propellant 227 or a mixture thereof, generally at about 50 : 50 w/w. More preferably the propellant consists of Propellant 134a.

The formulations may contain surfactant but are preferably free of surfactant. The formulations are preferably free of other excipients.

Preferred formulations consist of from 1 to 5 mg/ml ciclesonide, 8% by weight ethanol and Propellant 134a.

The formulations may be prepared by adding the required quantity of drug into an aerosol vial, crimping a valve on the vial and introducing a pre-mixed blend of propellant and ethanol through the valve. The vial is placed in an ultrasonic bath to ensure solubilisation of the drug.

5 Alternatively, the formulations may be prepared by preparing a drug concentrate with ethanol and adding this concentrate to the pre-chilled propellant in a batching vessel. The resulting formulation is filled into vials.

 The formulations may be filled in plastics, metal or glass vials. Suitable plastics materials include polyethyleneterephthalate; a preferred metal is
10 aluminium.

 The vials are equipped with a metered dose dispensing valve e.g. dispensing 50 μ l with each actuation. A suitable metered dose dispensing valve comprises a valve ferrule having a rim and associated rim gasket for engaging the aerosol vial and an aperture therethrough;

15 a metering tank having walls defining an exterior, an internal metering chamber, an inlet orifice, an inlet end, and an outlet end;

 an elongate valve stem having a filling channel, a filling end, a discharge end, and a discharge orifice;

 wherein the outlet end of the metering tank is in sealing engagement with
20 the valve ferrule, the discharge end of the valve stem passes through both the valve ferrule aperture and the outlet end of the metering tank and is in slidable sealing engagement with the valve ferrule;

 wherein the filling end of the valve stem passes through and is in slidable engagement with the inlet orifice of the metering tank, and a bottle emptier
25 surrounding the metering tank and filling end of the elongate valve stem and defining a passage between the metering tank and bottle emptier allowing communication between the inlet orifice of the metering tank and the aerosol vial;

 wherein the valve stem is movable between an extended closed position wherein the filling channel of the valve stem allows open communication, via the
30 inlet orifice, between the interior and the exterior of the metering chamber, and

wherein the outlet end of the metering tank is closed, and a compressed open position wherein the inlet orifice of the metering tank is in sealing engagement with the filling end of the valve stem and the discharge orifice of the valve stem allows open communication between the interior and exterior of the metering chamber.

A suitable valve is commercially available under the trade name SPRAYMISER.

The invention will now be described with reference to the accompanying drawings in which:

Figure 1 represents a cross-section through a metered dose dispensing valve suitable for use in the invention,

Figure 2 represents a longitudinal cross-section through an adaptor for accommodating an aerosol vial equipped with a metered dose dispensing valve, in accordance with the invention,

Figure 3 represents a front view of the adaptor shown in Figure 2, and, Figure 4 represents a detailed section of the area X shown in Figure 2.

The valve illustrated in Figure 1 comprises a valve ferrule (2) and an associated rim gasket (4) for engaging an aerosol vial. The rim gasket (4) may conveniently comprise an ethylene-butylene copolymer e.g. the copolymer commercially available from Union Carbide under the trade name FLEXOMER GERS 1085NT.

A metering tank (6) has walls defining a metering chamber (8) having an inlet end associated with a tank seal (10) and an outlet end associated with a diaphragm (12). An elongate valve stem (14) having a filling channel (16), a discharge end (18) and a discharge orifice (20) extends through the valve ferrule and metering chamber in sealing engagement with the diaphragm (12) and tank seal (10).

The tank seal and diaphragm may conveniently comprise a butadiene-acrylonitrile copolymer e.g. Type DB-218 commercially available from American Gasket & Rubber Company.

A bottle emptier (22) surround the metering tank (6) and valve stem such that a capillary channel (24) is defined between the metering tank and bottle emptier to allow passage of aerosol formulation from the aerosol vial to the inlet end of the metering chamber.

5 The valve stem (14) is movable between an extended closed position wherein the filling channel (16) of the valve stem allows open communication, via the inlet orifice, between the interior and the exterior of the metering chamber, and wherein the outlet end of the metering tank is closed, and a compressed open position wherein the inlet orifice of the metering tank is in sealing engagement
10 with the filling end of the valve stem and the discharge orifice of the valve stem allows open communication between the interior and exterior of the metering chamber. The valve stem (14) is biased to the extended closed position by spring (15).

 Figures 2 to 4 illustrate a press-and-breathe adaptor for an aerosol vial
15 equipped with dispensing valve suitable for use in the invention. The adaptor comprises a body portion (30) and a mouthpiece (32). A plurality of ribs (34) are positioned within the body portion (30) in order to locate and support the aerosol vial (not shown) in the correct position. The dispensing end of the elongate valve stem of the metered dose dispensing valve is positioned within the nozzle block
20 (36). The adaptor is made of polypropylene or high density polyethylene. However, to ensure a good seal between the valve stem (14) and the central aperture (38), high density polyethylene is preferred.

 As shown in Figure 4 the nozzle block (36) comprises a central aperture (38) having a flared opening (40) to accommodate the valve stem. The valve stem
25 is inserted until it abuts the ledge (42). In use, the patient inserts the mouthpiece into the mouth and depresses the base of the aerosol vial while inhaling. The relative movement between the elongate valve stem and the metering tank causes the discharge orifice to enter the metering tank and the contents thereof are dispensed under pressure through the discharge end of the elongate valve stem to
30 enter chamber (44) in the nozzle block (36) and exit through orifice (46). A plume

of droplets of respirable size is directed from the orifice (46) into the mouthpiece (32) for inhalation by the patient.

It has been found that the dimensions of the orifice (46) may have a profound effect on the respirable fraction of the formulation dispensed from the mouthpiece of the adaptor. Both the jet length "l" and diameter "d" of the orifice (46) affect the delivery to the lung of the formulation. This is often assessed by an "in vitro" test which uses an Andersen Cascade Impactor, such as described in the U.S. Pharmacopoeia. An Andersen Respirable Dose is defined as the weight of drug delivered to plates 3 to 7 and the filter of the impactor from a single actuation of the inhaler. The optimum dimensions are also dependent upon the particular formulation to be dispensed. In general, medication delivery increases with increasing orifice diameter "d" and with increasing jet length "l". However, the Anderson respirable dose increases with decrease in orifice diameter "d".

The selection of particular dimensions of the nozzle orifice enables an Andersen Respirable Dose of greater than 120 micrograms to be achieved for a product delivering 200 micrograms of ciclesonide per actuation ex valve, without significantly detracting from the Medication Delivery. Thus the patient potentially derives the benefit of a higher than usual proportion of dispensed drug reaching the lungs without excessive build-up of drug on the actuator or the product falling short of regulatory stipulations.

For formulations containing from 5 to 10% by weight ethanol, particularly 8% by weight ethanol it has been found that good respirable doses are achieved with an orifice diameter "d" within the range 0.20 to 0.33mm, preferably about 0.28mm and a jet length "l" in the range 0.30 to 0.60mm preferably 0.50mm.

The invention will now be illustrated by the following Examples:

In each Example, the percentage of ethanol in the ethanol/propellant blend is denoted in brackets.

Example 1

	mg/ml
Ciclesonide	1.000
Ethanol (5%)	67.800
P227	1287.200
	1356.000

Example 2

	mg/ml
Ciclesonide	5.000
Ethanol (5%)	67.800
P227	1283.200
	1356.000

5

Example 3

	mg/ml
Ciclesonide	1.000
Ethanol (20%)	244.800
P227	978.200
	1224.000

Example 4

	mg/ml
Ciclesonide	5.000
Ethanol (20%)	244.800
P227	974.200
	1224.000

Example 5

	mg/ml
Ciclesonide	1.000
Ethanol (7%)	82.740
P134a	1098.260
	1182.000

Example 6

	mg/ml
Ciclesonide	5.000
Ethanol (7%)	82.740
P134a	1094.260
	1182.000

5

Example 7

	mg/ml
Ciclesonide	1.000
Ethanol (20%)	220.800
P134a	882.200
	1104.000

Example 8

	mg/ml
Ciclesonide	5.000
Ethanol (8%)	220.800
P134a	878.200
	1104.000

Example 9

	mg/ml
Ciclesonide	1.000
Ethanol (8%)	102.160
P227	586.920
P134a	586.920
	11277.000

Example 10

	mg/ml
Ciclesonide	5.000
Ethanol (8%)	102.160
P227	584.920
P134a	584.920
	11277.920

5

Example 11

	mg/ml
Ciclesonide	1.000
Ethanol (12%)	126.500
P227	568.750
P134a	568.750
	1265.000

Example 12

	mg/ml
Ciclesonide	5.000
Ethanol (120i)	126.500
P227	566.750
P134a	566.750
	1151.000

Example 13

	mg/ml
Ciclesonide	1.000
Ethanol	94.800
P134a	1090.200
	1186.000

5

Example 14

	mg/ml
Ciclesonide	2.000
Ethanol	94.7200
P134a	1089.280
	1186.000

Example 15

	mg/ml
Ciclesonide	4.000
Ethanol	94.5600
P134a	1087.440
	1186.000

Example 16

	mg/ml
Ciclesonide	4.000
oleic acid	0.237
Ethanol	94.541
P134a	1087.222
	1186.000

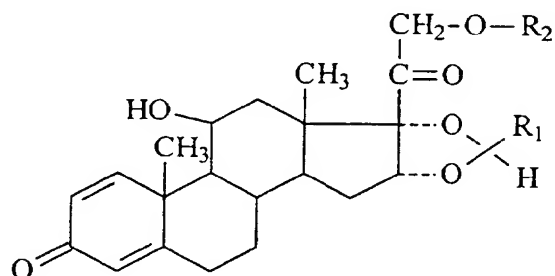
All of the formulations of Examples 1 to 15 were clear, colourless solutions in which the ciclesonide was completely solubilized.

5 Examples 13 to 15 were the subject of stability trials over several months and proved to be physically and chemically stable.

 Although the invention has been described in terms of preferred formulations and ingredients, it will be understood that these are not intended to be limiting. To the contrary, those skilled in the art will understand that various
10 optional ingredients may be included, such as flavoring agents, preservatives, additional active ingredients, and the like, while still embodying the present invention.

CLAIMS

1. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula:



in which:

R_1 is 1-butyl, 2-butyl, cyclohexyl or phenyl and

R_2 is acetyl or isobutanoyl, and a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof, and ethanol in an amount effective to solubilize the compound of formula (I) and optionally a surfactant.

2. A pharmaceutical composition as claimed in Claim 1 in which the compound of formula (I) is ciclesonide.

3. A pharmaceutical composition as claimed in Claim 1 which is free of surfactant.

4. A pharmaceutical composition as claimed in Claim 1 in which the composition comprises from 3 to 25% by weight of ethanol.

5. A pharmaceutical composition as claimed in Claim 4 in which the composition comprises from 5 to 20% by weight of ethanol.

6. A pharmaceutical composition as claimed in Claim 5 in which the composition comprises from 7 to 12% by weight of ethanol.

7. A pharmaceutical composition as claimed in Claim 6 in which the composition comprises 8% by weight of ethanol.

8. A pharmaceutical composition as claimed in Claim 2 comprising from 1 to 8 mg/ml of ciclesonide.

9. A pharmaceutical composition as claimed in Claim 1 in which the propellant is 1,1,1,2-tetrafluoroethane.

10. A pharmaceutical composition as claimed in any Claims 1 in which the propellant is 1,1,1,2,3,3,3-heptafluoropropane.

11. A pharmaceutical composition as claimed in Claim 9 consisting of ciclesonide at a concentration of 1 to 5mg/ml in a blend of ethanol : 1,1,1,2-tetrafluoroethane with a ratio 8 : 92 by weight.

12. A pharmaceutical product comprising an aerosol vial equipped with a dispensing valve and containing a formulation as claimed in Claim 1.

13. A pharmaceutical composition as claimed in Claim 12 in which the valve is a metered dose dispensing valve.

14. A pharmaceutical composition as claimed in Claim 13 in which the valve comprises a valve ferrule having a rim and associated rim gasket for engaging the aerosol vial and an aperture therethrough;

a metering tank having walls defining an exterior, an internal metering chamber, an inlet orifice, an inlet end, and an outlet end;

an elongate valve stem having a filling channel, a filling end, a discharge end, and a discharge orifice;

wherein the outlet end of the metering tank is in sealing engagement with the valve ferrule, the discharge end of the valve stem passes through both the valve ferrule aperture and the outlet end of the metering tank and is in slidable sealing engagement with the valve ferrule;

wherein the filling end of the valve stem passes through and is in slidable engagement with the inlet orifice of the metering tank, and a bottle emptier surrounding the metering tank and filling end of the elongate valve stem and defining a passage between the metering tank and bottle emptier allowing communication between the inlet orifice of the metering tank and the aerosol vial;

wherein the valve stem is movable between an extended closed position wherein the filling channel of the valve stem allows open communication, via the inlet orifice, between the interior and the exterior of the metering chamber, and wherein the outlet end of the metering tank is closed, and a compressed open position wherein the inlet orifice of the metering tank is in sealing engagement with the filling end of the valve stem and the discharge orifice of the valve stem allows open communication between the interior and exterior of the metering chamber.

15. A pharmaceutical product as claimed in Claim 14 additionally comprising an adapter having a body for containing the aerosol vial, a nozzle block accommodating the discharge end of the valve stem and a mouthpiece.

16. A pharmaceutical product as claimed in Claim 15 in which the nozzle block has an exit orifice directed towards the mouthpiece, the exit orifice having a diameter in the range 0.20 to 0.33mm.

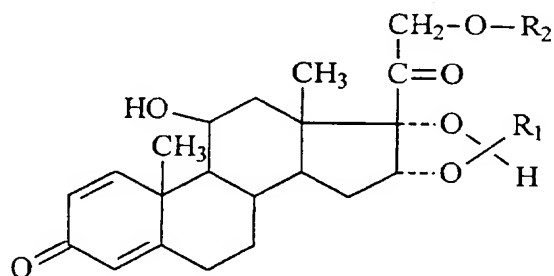
17. A pharmaceutical product as claimed in Claim 16 in which the exit orifice has a diameter of about 0.28mm.

18. A pharmaceutical product as claimed in Claim 17 in which the exit orifice has a jet length in the range 0.30 to 0.60mm.

5 19. A pharmaceutical product as claimed in Claim 18 in which the exit orifice has a jet length of 0.50mm.

20. A pharmaceutical aerosol formulation contained in an aerosol canister equipped with a dispensing valve, the formulation comprising:

10 a compound of the
formula:



in which:

R₁ is 1-butyl, 2-butyl, cyclohexyl or phenyl and

15 R₂ is acetyl or isobutanoyl;

a hydrofluorocarbon propellant; and

cosolvent in an amount effective to solubilize the compound of formula (I).

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/10155

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/00 A61K31/48

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 247 680 A (ESPECIALIDADES LATINAS MEDICAMENTOS UNIVERSALES) 11 March 1992 cited in the application see the whole document ---	1-20
A	DE 195 41 689 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 15 May 1996 see the whole document -----	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

20 August 1998

Date of mailing of the international search report

26/08/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/10155

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2247680 A	11-03-1992	AT 402930 B	25-09-1997
		AT 176991 A	15-02-1997
		AU 649472 B	26-05-1994
		AU 8368691 A	12-03-1992
		BE 1005876 A	22-02-1994
		CA 2050812 A	08-03-1992
		CH 683343 A	28-02-1994
		DE 4129535 A	12-03-1992
		ES 2034893 B	01-01-1994
		FR 2666585 A	13-03-1992
		GR 91100353 A,B	11-09-1992
		IT 1251376 B	09-05-1995
		JP 4257599 A	11-09-1992
		LU 88001 A	01-06-1992
		NL 9101472 A	01-04-1992
		PT 98897 A	31-07-1992
		US 5482934 A	09-01-1996
DE 19541689 A	15-05-1996	NONE	